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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/424,705	06/02/00	LITTLE M	35280047US00

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	13

DATE MAILED: 05/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/424,705	LITTLE ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment, filed 3/6/01 (Paper No. 11), is acknowledged.
Claims 10-11 have been canceled.
Claims 1-9 *are pending.*

2. Applicant's election of Group I, claims 1-9 in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

However, given the cancellation of claims 10-11, the restriction requirement is rendered moot.

Claims 1-9 *are under consideration in the instant application.*

3. Sequence compliance: The instant application is in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). *Applicant should amend the first line of the specification to indicate priority is claimed under 35 U.S.C. 371 to PCT/DE98/01409.*

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

7. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

8. The references cited in the Search Report have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed within the set period for reply to this Office action.

9. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(e) Brief Summary of the Invention.
(f) Brief Description of the Several Views of the Drawing(s).
(g) Detailed Description of the Invention.
(h) Claim or Claims (commencing on a separate sheet).
(i) Abstract of the Disclosure (commencing on a separate sheet).
(j) Drawings.
(k) Sequence Listing (see 37 CFR 1.821-1.825).

10. The disclosure is objected to because of the following informalities: on page 6 at line 18 (last line of 2nd paragraph) a SEQ ID NO: is required. This sequence appears to correspond to SEQ ID NO:7; Appropriate correction is required.

11. The disclosure is objected to because of the following informalities: the ATCC address on page 1 of the specification is not current. The current ATCC address is
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.
Appropriate correction is required.

12. Claim 4b is objected to because of the following informalities: the phrase "by means of PCR" is atypical claim language. It is suggested that Applicant delete the phrase. Appropriate correction is required.

13. Claims 4-9 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiply dependent claim. See MPEP § 608.01(n).

14. Claims 1, 3, 5 and 7 are objected to under 37CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claims.

15. The following is noted:
Claims 1-3 recite a "monoclonal antibody" and claims 4-9 a method for the production of a "monoclonal antibody". The term "monoclonal antibody" is not explicitly defined in the specification; but the specification on page 1 in the 2nd paragraph defines OKT3 as a monoclonal IgG2a-type antibody. IgG2a antibodies possess constant regions – this is what allows an assignment to the IgG2a subclass. Therefore, the term "monoclonal antibody" reads on full length antibodies having constant regions. Based upon this definition of OKT3, several rejections are set forth under 35 USC 112, second paragraph.

However, the method steps presented in the body of claims 4-9 and in the specification appear to be limited to the production of a single chain Fv. Therefore for the purposes of examination under 35 USC 102 and 103 the claims are interpreted as limited to a single chain Fv.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-9 contain the trademark/trade name OKT3. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a particular antibody and, accordingly, the identification/description is indefinite.

It is suggested that Applicant amend the claims to include a recitation of the ATCC deposit number CRL 8001, as disclosed on page 1 of the specification.

B) Claims 1-9 are indefinite in reciting "position H100A of the OKT3 antibody". The disclosure does not provide a numbered reference sequence. Neither is it clearly disclosed that there is only a single sequence encompassed by the claim since, as discussed supra, "OKT3" is a trademark and as such is indefinite.

It is suggested that Applicant incorporate into the claim both the ATCC deposit number AND the numbering system used (e.g., "according to the Kabat numbering system" as disclosed on page 3).

C) Claims 1-9 ambiguous in that it is not clear if position H100A of the OKT3 antibody has the Cys to Ser exchange on one, or both of the heavy chains. The specification on page 1 in the 2nd paragraph defines OKT3 as a monoclonal IgG2a-type antibody. IgG2a antibodies have two heavy chains. Therefore, the language of claim 1 is ambiguous.

It is noted that if claim 1 recited a single chain Fv, as disclosed in the example; then there would be no ambiguity since a single chain Fv has only one "position H100A".

D) Claims 2-3 recite the limitations "The monoclonal antibody" and "the polar amino acid". There is insufficient antecedent basis for these limitations in the claim.

It is suggested that Applicant either amend claim 2 to depend from claim 1, or rewrite the claim to indicate "A" rather than "The", and to provide proper antecedent basis within the claim for "the polar amino acid", possibly by incorporating the language of claim 1.

E) Claims 4-9 recite a method for the production of the monoclonal antibody according to any one of claims 1-3; however, the method steps of claims 4-9 only result in the production of a recombinant antibody that lacks constant regions (such as a single chain Fv), since step 4b only provides for the amplification of the variable domains of the light and heavy chains. Thus there are essential steps missing from claims 4-9 needed for the production of the monoclonal antibody of any of claims 1-3.

Since it does not appear that Applicant can provide the requisite steps based on the disclosure, it is suggested that Applicant limit claims 1-3 to recite a single chain Fv antibody, as supported by the Example and the method steps of claims 4-9.

F) Claims 4b, and 6-9 recite the limitation "suitable primers". The metes and bounds of this phrase are unclear.

It is suggested that Applicant amend claim 4b to recite either specific primers, such as those recited in claim 5, or to provide language indicating the region amplified, e.g., "using primers which hybridize to the amino-terminal part of the constant domains and which hybridize to the FR1 region", as supported on page 5, or similar language.

G) In claim 4c and dependent claims 5-9, the recitation of "the desired mutation" is a relative term which renders the claims indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

It is suggested that Applicant limit the mutation as set forth in claim 1.

H) Claims 8 and 9 are indefinite in the recitation of "pHOG21" because its characteristics are not known. The use of "pHOG21" as the sole means of identifying the claimed vector renders the claims indefinite because the name is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct vectors.

Amending claim 8 to recite an ATCC Accession Number would obviate this rejection.

I) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. It is apparent that the hybridoma CRL 8001 which produces the OKT3 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent vector. See 37 CFR 1.801-1.809.

However, it is noted that CRL 8001 is publicly available from ATCC as shown by the attached entry for CRL 8001 (ATCC Cell Lines and Hybridomas, page 393, 8th edition, 1994 American Type Culture Collection, current address 10801 University Boulevard, Manassas, VA 20110-2209); therefore the enablement requirement with respect to CRL 8001 which produces the OKT3 antibody appears to be satisfied.

20. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the pHOG21 vector is required to practice the claimed invention. As a required element, it must be known *and readily available to the public or obtainable by a repeatable method set forth in the specification.* If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent vector. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, Applicant is required to assure that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent" as per 37 CFR 1.808 (a)(2).

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. NOTE THAT THE CURRENT ATCC DEPOSITORY ADDRESS is American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209. As an additional means for completing the record, Applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

21. Claims 4-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "exchange of Cys to Ser at position H100A", does not reasonably provide enablement for "desired mutation". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. A person of skill in the art is not enabled to make and use OKT3 antibodies with a "desired mutation" as encompassed by the full breadth of the claim as currently recited. There is insufficient guidance in the specification to direct a person of skill in the art in how to make and use an OKT3 antibody with *any* "desired mutation", other than a mutation which is an "exchange of Cys to Ser at position H100A". The term "desired mutation", as recited, encompasses *any* mutation in the OKT3 antibody and does not sufficiently indicate a functional readout to ascertain if the mutation is a "desirable" rather than undesirable mutation.

It was well known by the skilled artisan at the time the invention was made that the effect of mutating individual antibody residues was unpredictable. Single amino acid changes can have profound impact on antigen specificity to either enhance or abolish binding. For example, Radic and Seal (Methods: A companion to Methods in Enzymology 1997;11:20-26) teach that changing a single amino acid (R53 of VH3H9) eliminates binding to its antigen dsDNA (see entire document, especially page 22, 1st column, 2nd full paragraph). Therefore, without direction both to particular residues for introduction of mutations, guidance as to what those residues should be changed to (at least in general terms), and an indication of the function that is to be maintained or improved; it would require undue experimentation of the skilled artisan to make and use an OKT3 antibody with a "desired mutation" as currently recited.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Since it is unpredictable as to which other "desired mutations" could be made and still maintain the (unrecited) functional properties of the OKT3 antibody; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Kipriyanov et al. (Protein Engineering April 1997; 10:445-453, see entire document).

Kipriyanov et al. teach a monoclonal scFv antibody in which the cysteine at position H100A of the OKT3 antibody has been exchanged with the polar amino acid serine (see entire document, especially page 448 "Construction and expression of anti-CD3 scFv mutants"). Kipriyanov et al. also teach that the antibody has the sequence of Figure 2 of the instant application (see especially Figure 2B of reference). Finally, Kipriyanov et al. teach a method of producing the monoclonal scFv antibody with the C->S exchange at position H100A using the method steps recited in claims 4-9, including each limitation with respect to the primers (claim 5), pCR-Skript SK(+) vector (claim 6), SK1 primer (claim 7), pHOG21 vector (Claim 8), and expression in XL1-Blue (claim 9) (see entire document, in particular the Materials and Methods on page 446 for "Cloning of the variable regions", "Construction of plasmids encoding scFv", "Construction of anti-CD3 mutants", and "E. coli expression and purification of scFv fragments").

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the prior art scFv antibody and the method of making said antibody.

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 1-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroon et al. (Pharmaceutical Res. 9:1386-1393 1992) in view of Kipriyanov et al. (J. Immunol. Meth. 1996; 196:51-62) and in further view of Senoo et al (US Pat. No. 5,852,177).

The claims are drawn to an OKT3 antibody in which the cysteine at position H100A has been exchanged with a polar amino acid, and a method of producing this antibody.

Kroon et al teach that the OKT3 antibody is inactivated while in storage as a consequence of formation of cross-links between heavy chain in the region of amino acids 99-121 (see entire document, especially page 1391-1392 bridging paragraph and the sequence of Figure 1). Although the numbering system used is different, Kroon et al. teach that the Cys in the third heavy chain CDR is a likely candidate for oxidation which would lead to degradative structural changes for OKT3 (see especially page 1390). Kroon et al. further teach that using site directed mutagenesis to synthesize analogues that are more stable would be beneficial for the development of therapeutics (e.g., page 1392, last paragraph).

Kroon et al. do not teach an explicit method of producing a mutated OKT3 antibody, or the mutated OKT3 antibody.

Kipriyanov et al. teach a method of producing scFv from hybridomas of interest by obtaining mRNA, transcribing the mRNA to cDNA, amplifying the heavy and light chain variable regions using the primers Bi5, Bi8, Bi4, and Bi3f, cloning the amplified DNA into the pCR-Skript SK(+) vector adapted for site-specific mutagenesis, insertion of the DNA into the expression vector pHOG21, and finally expression of the scFv using E. Coli XL1-Blue (see entire document, especially sections 2.2 to 2.5).

Senoo et al. teach that formation of intra and interchain disulfide bonds is detrimental to protein stability (see entire document, especially column 1 to column 2, bridging paragraph) and that the conversion of a cysteine to serine to eliminates this problem and improves protein stability (e.g., column 7, lines 55-57).

Therefore it would have been obvious to one of ordinary skill in the art to apply the teachings of Kipriyanov et al and Senoo et al. to the teachings of Kroon et al. to obtain an OKT3 antibody in which heavy chain cysteine 100A (in the instant numbering system) was replaced with serine in order to produce a more stable OKT3 antibody. Site-directed mutagenesis to produce such a molecule was well within the skill of the ordinary artisan at the time the invention was made. Primer selection and design, based upon a known sequence, would have been a matter of selection based upon the sequence to be mutated. Kroon et al. give clear direction to the region of H100A, which is the Cys found in the third CDR of the heavy chain. Senoo et al. teach that mutagenesis to Ser eliminates disulfide bonding detrimental to stability. Given the teachings of the references, the ordinary artisan would have had a reasonable expectation of producing a mutated OKT3 scFv in which the Cys in CDR3 (H100A) had been exchanged for cysteine. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

26. No claim is allowed.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
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May 7, 2001

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